

Losing Years of Human Life in Heavy Polluted Cities in Macedonia

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Abstract

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INTRODUCTION: The urban air pollution will deteriorate globally, by 2050 outdoor particulate air pollution and ground-level ozone is projected to become the top cause of environmentally related deaths worldwide.

AIM: To assess the burden of diseases due to particulate air pollution and health benefits from the pollution reduction policies.

METHODS: Environmental burden of disease methodology has been applied. Environmental data for population exposure, total years of life lost from all causes, and relevant concentration-response functions have been used in estimation.

RESULTS: The estimated disease burden from all causes (excl. external) is 30,256 YLL (19,436-40,625 95% CI) in Skopje Region, and 10,343 YLL (6,224-14,785 95% CI) in Tetovo. In terms of cardiopulmonary mortality, the estimated disease burden is 9,282/100,000 in Tetovo, in the Skopje Region 3,784/100,000 respectively. Annually in Tetovo 1,645 years of healthy life are lost, while in the Skopje Region 3,936 due to lung cancer premature mortality. The estimated health gain is significant, for the three selected health outcomes if EU limit values are reached, 41-42% of the estimated burden in Skopje Region will be eliminated, and 74-77% in Tetovo.

CONCLUSION: the estimated impact of particulate air pollution on mortality is significant and not negligible. The same applies to the health and well-being of the population if the EU or WHO limit levels are reached.

Introduction

The Global Burden of Diseases Study (GBD; 2015) estimates that pollution-related disease was responsible for 9 million premature deaths in 2015, presenting 16% of total global mortality. Out of it, 4.2 million (3.7–4.8) premature deaths are attributable to ambient particulate air pollution, whereas 2.9 (2.2–3.6) due to indoor air pollution [1]. According to the World Health Organization (WHO), in the European region of the WHO, the exposure of suspended particles is responsible for reducing every person's life

expectancy by an average of almost a year, mainly due to the increased risk of cardiovascular, respiratory diseases and lung cancer [2].

Air pollution emphasizes the inequalities, disproportionately affecting mostly the poorest and vulnerable group's particularly children. Children are affected even at low-dose exposures to pollutants during the windows of vulnerability in utero and early infancy as well. Disease caused by pollution is most prevalent among minorities and the marginalised [3]. Air pollution often serves as an indicator of the economically sustainable development of a country because sources of air pollution are also the main

producers of substances that are major climate modifiers such as carbon dioxide, black carbon etc. Sustainable Development Goal (SDG 11) refers to the target to make cities inclusive, safe, resilient and sustainable. Annual mean levels of fine particulate matter in cities indicates the sustainable urban development. Also, SDG3 refers to the provision of healthy living and well-being for all. Mortality rate attributed to household and ambient air pollution is a direct indicator of the progress toward this target [4]. Achieving the pollution control, the health and well-being benefits will be significant, climate change pace will be slowed down, and social justice promoted.

However, the urban air pollution will deteriorate globally, by 2050 outdoor particulate air pollution and ground-level ozone is projected to become the top cause of environmentally related deaths worldwide [5]. Primarily, at risk are people in urban areas. 30% of the urban population in EU are exposed to air pollution levels exceeding EU standards and 98% citizens living in European cities that exceed more stringent WHO guidelines for air quality [6], [7]. There is no evidence of a safety thresholds of PM concentration [8], and EU standards are not sufficiently stringent to protect human health [9].

The large scientific evidence for health impact of air pollution is already built, starting with the Harvard Six-Cities study [9], ACS (American Cancer Society) study [10] from the beginning of 1990s that have established a permanent positive association between long-term exposure to air pollution and total cardiovascular mortality (mainly due to coronary artery disease), and continuing with the European studies such as the Dutch study and following ones [11]. Approximately 71% of the total burden of disease account to non-communicable diseases (NCDs) [12]. Deaths related to cardiovascular disease (ischaemic heart disease, stroke), chronic obstructive pulmonary disease and lung cancer poses a great burden to the health systems and societies in general [13], [14], [15], [16], [17], [18].

Still, there is insufficient evidence from the countries of the Former Yugoslav republics and region in general. Converting lost years of life and disabilities to DALYs (or Disability-adjusted Life Years), the World Bank Study in 2011 estimated health effects of air pollution in Macedonia that represent an annual economic cost of €253 million or 3.2 per cent of GDP. Savings from reducing the levels of particulate matters in the country will be significant, 151 million per year will be saved, and over 800 deaths and thousands of days in lost productivity will be avoided [19]. The latest study indicates 1205 attributable deaths (819-1538 95% CI) due to PM_{2.5} exposures in the Skopje Region, and 265 attributable deaths (187-327 95% CI) in Tetovo, the most polluted cities in the country [20].

Based on the decade long monitoring of air pollution concentration, nowadays it is well known that

urban air pollution is a significant problem in the country. The mountainous terrain and meteorological conditions cause extra challenges for the national air pollution management. Many sources have been identified: traffic (poorly maintained vehicle fleet), domestic heating, energy production relies mostly on poor-quality lignite in old thermal power plants, the absence of proper waste management etc. [21]. Based on the broad scientific evidence and knowledge, is expected that current exposures on particulate air pollution will lead to further deterioration of the health status of population, causing a variety of adverse and harmful health effects and great economic losses due to increased need of health care services, increased medication use, absenteeism from work and school, restricted activity and losses due to premature deaths and active years of life.

Material and Methods

Aiming to assess the burden of diseases due to particulate air pollution and most importantly to assess the health benefits from implementation of effective and consistent measures and policies that would reduce the concentration of the stressors to the EU limit values (EU LV), we have applied a method for assessing disease burden that was firstly developed in the 1980s by WHO and other HIA studies [22], [23], [24], [25], using a YLL (Years of Life Lost) as a selected metrics for quantification of the disease burden. The data for the YLL due to premature mortality are obtained from the WHO Global Health Estimates (WHO GHE, 2016) database. Environmental data for population exposure of PM_{2.5} obtained from the National Air Quality Monitoring Network run by Ministry of Environment and Physical Planning (MoEPP) have been used, and relevant Concentration-response Functions (CRFs) have been applied.

The epidemiological concept *Population Attributable Fraction (PAF)* assess "the proportional reduction in the outcome incidence if all risk factors of interest were simultaneously eliminated from the target population" [26], [27]. It has been applied and calculated using the following formula:

Equation 1. Calculation of PAF

$$PAF = \frac{f \times (RR - 1)}{f \times (RR - 1) + 1}$$

Then we assess the environmental burden of disease due to PM_{2.5} exposures using the following formula:

Equation 2. Calculation of environmental burden of disease

$$EBoD = PAF \times BoD$$

Eventually, we have estimated the years of life lost that could be avoided if the EU LV is achieved by the implementation of the consistent policies and actions, using EU LV for PM_{2.5} as a cut-off value (25 µg/m³).

Basic demographic data

Distribution of the population by the age groups and sex were obtained from the State Statistical Office (SSO). In the study, we have used the Population Projections of the SSO for 2017 [28] (Table 1). The total population of the selected cities (Skopje Region and Tetovo) is considered as a target population. The City of Skopje is a capital city and separate unit of the local self-government, consisting 10 urban municipalities, while the Skopje Region comprised seven more rural municipalities. Regarding Tetovo, the total population of the urban and 19 rural municipalities is included in this study [29]. We have selected those two cities due to the highest population exposures on particulate air pollution that exceed EU significantly and WHO limit values particularly during the cold season.

Table 1: Distribution of the population by the age groups in the selected cities

Age groups	Skopje region		Tetovo		Macedonia	
	#	% of total population	#	% of total population	#	% of total population
0-24	190,266	30.3	30,469	33.0	605,255	29.2
25-64	345,637	55.1	52,634	57.1	1,186,597	57.2
65 and over	91,595	14.6	9,098	9.9	283,256	13.6
Unknown	60	0.01	15	0.0	193	0.01
TOTAL	627,558		92,216		2,075,301	

Source: MAKStat database. SSO, 2018.

Environmental data

We have used an annual mean concentration of PM₁₀ and PM_{2.5} from six monitoring stations for the Skopje Region and one located in Tetovo. For calculation of the national mean value of PM_{2.5}, the average of all seventeen monitoring stations has been used. To avoid the variation of the concentration of selected stressor due to some partial policies or meteorological factors, we used the five-years average for the period 2012-2016 (Table 2).

Table 2: Annual mean concentration of PM₁₀ for the period 2012-2016

Monitoring point	PM ₁₀ (µg/m ³)					5-year average
	2012	2013	2014	2015	2016	
Skopje region Karpos (UB), Centar (UT), Gazi Baba (SUB), Lisice (I) Rektorat (UT) and Miladinovci (R)	86.8	73.4	68.7	66.6	65.7	72.2
Tetovo Tetovo (UT)	133.3	140.9	133.8	147.2	96.9	130.4
MKD	83.9	68.8	62.5	63.8	54.0	66.6

UB-urban background; UT-urban traffic; SUB-suburban background; I-industrial, UT-urban traffic; R-refinery; Source: Macedonian Environmental Information Center (MEIC), MoEPP, 2017.

Only two monitoring stations in the Skopje Region continuously monitors the concentration of PM_{2.5}. The annual mean concentration of PM_{2.5} in

Tetovo and the national average is based on calculation (Table 3). HRAPIE study (Health risk of air pollution in Europe) formula is applied, whereas PM_{2.5} are calculated as a fraction of the total mass of measured PM₁₀ (PM_{2.5}/PM₁₀ ratio = 0.65)

Table 3: Annual mean concentration of PM_{2.5} for the period 2012-2016

	PM _{2.5} (µg/m ³)					5-year average
	2012	2013	2014	2015	2016	
Skopje region	51.4	40.7	39.2	44.4	33.0	41.8
Tetovo ^e	86.7	91.6	87.0	95.7	63.0	81.7
MKD ^e	56.8	54.0	44.7	45.2	38.2	45.9

^e (estimation); Source: Macedonian Environmental Information Center (MEIC), MoEPP, 2017.

Years of Life Lost, from the WHO database (GHE; 2016)

The data for the YLL due to premature mortality (for the age group 30 and over) have been obtained from the WHO Global Health Estimates (GHE; 2016) database. Three health outcomes were selected for the burden quantification and assessment of the health benefit: All-cause (natural) mortality (excluding external causes); cardiopulmonary and lung cancer mortality.

Concentration-response functions (CRFs)

Health Impact Assessment approach, in general, apply CRFs mostly expressed in terms of Relative Risk (RR) for a unit change in concentration, estimated in the numerous epidemiological studies. These functions are used to link the exposure to air pollution and scenarios for changes in the air quality of the population at risk, as well as its basic health status [30]. The CRFs used in this paper for the selected health outcomes with Confidence Intervals of 95% (95% CI) are shown in Table 4.

Table 4: Summary of the relative risk (RR, 95% CI) applied in the study for PM_{2.5} as a selected stressor

Stressor	Health endpoint	Age group	ICD10 code	Unit of exposure	Point estimate of CRF	LCL (95% CI)	UCL (95% CI)	Reference(s)
PM _{2.5}	All-cause (natural) mortality	Adult (>30 yr)	A00-R99	10 µg/m ³	1.062	1.040	1.083	Heroux et al. 2015 [31] Meta-analysis of 13 cohort studies: Hoek et al. (2013) [32] Pope et al., 2002 [33].
PM _{2.5}	Cardiopulmonary mortality	Adult (>30 yr)	I00-I99	10 µg/m ³	1.0797	1.0202	1.1401	WHO, 2006a
PM _{2.5}	Lung cancer	Adult (>30 yr)	C32-C34	10 µg/m ³	1.1267	1.0407	1.2190	Pope et al., 2002 [33] WHO, 2006a

Results

Using YLL due to premature mortality as a selected metrics in this study, we aimed to assess not only the environmental burden of disease due to PM_{2.5} but estimation of the benefits of implementation of targeted public health policies and actions and policies in other sectors was from our great

importance. The ultimate objective will be a creation of the targeted public health policies and policies in the other sectors that would reduce the disease burden due to current exposures.

For that purpose, several tables (Table 5, 6, and 7) were prepared for three selected health outcomes: all-cause (natural) mortality where external causes have been excluded; mortality from cardiorespiratory diseases, and lung cancer deaths. The estimation uses YLL data for the age group of 30 years and more that corresponds to the relative risk estimates in Table 4, expressed for the same group.

Table 5: Years of life lost due to premature mortality in terms of all-cause (natural) mortality

Health endpoint - All-cause mortality (excl. External causes of death), stressor PM _{2.5}									
Region	Estimated YLL (000) (WHO GHE 2016), >30 yr.	5-yrs mean PM _{2.5} (µg/m ³)	RR Macedonian exposures (10 µg/m ³)	Population Attributable Fraction (PAF)	Estimated burden of disease -YLL			Years of life saved if the annual mean of PM _{2.5} is reduced to 25 µg/m ³ (EU LV)*	
					#	LCL 95%CI	UCL 95%CI		
Skopje region	380.7	41.8	1.29	0.08	30,256	19,436	40,625	12,470	
Tetovo	380.7	81.7	1.64	0.03	10,343	6,224	14,785	7,644	
MKD	380.7	45.9	1.32	0.24	91,851	62,720	116,679	38,696	

*EU LV (EU Limit values, EU Directive 2008/50/EC on ambient air quality and cleaner air for Europe).

The estimated disease burden from *all causes* (ICD10 code A00-Y89, excl. external causes of death V01-Y89) expressed as YLL is highest in Tetovo, where 10,343 years of healthy life are lost annually due to current exposure to PM_{2.5} (11,216/100,000). In the Skopje Region, the rate is 4821/100,000 while the national average is 4426/100,000 inhabitants (Table 5). The estimated *health benefits* observing all-cause natural mortality (except external), the number of saved years of healthy life in Tetovo will be 8,289/100,000, in the Skopje Region by 1987 and Macedonia with 1865/100,000 inhabitants.

Regarding the second selected health outcome - *Mortality from cardiopulmonary diseases* (ICD10 code I00-I99 and J00-J99), the estimated disease burden is 9,282/100,000 inhabitants in Tetovo, in the Skopje Region 3,784 whereas the national average is 3,315/100,000 inhabitants (Table 6).

Table 6: Years of life lost due to premature mortality in terms of cardiopulmonary mortality

Health endpoint - Cardiopulmonary mortality, stressor PM _{2.5}									
Region	Estimated YLL (000) (WHO GHE 2016), >30 yr.	5-yrs mean PM _{2.5} (µg/m ³)	RR Macedonian exposures (10 µg/m ³)	Population Attributable Fraction (PAF)	Estimated burden of disease -YLL			Years of life saved if the annual mean of PM _{2.5} is reduced to 25 µg/m ³ (EU LV)*	
					#	LCL 95%CI	UCL 95%CI		
Skopje region	231.8	41.8	1.38	0.10	23,749	5,941	41,874	9,840	
Tetovo	231.8	81.7	1.87	0.04	8,559	1,795	18,052	6,423	
MKD	231.8	45.9	1.42	0.30	68,792	20,312	104,829	28,344	

*EU LV (EU Limit values, EU Directive 2008/50/EC on ambient air quality and cleaner air for Europe).

Regarding cardiopulmonary mortality expressed per 100,000 population, the number of years of healthy life that would be saved is 6965, 1568 and 1366 for Tetovo, Skopje region and Macedonia.

Due to the linear association between the concentrations of PM_{2.5} and the observed health

outcome (in this case, *lung cancer mortality* (ICD10 code C32-C34)), again the highest in the rate of years of healthy life lost per 100,000 populations in Tetovo (1784); following Skopje Region and Republic of Macedonia (627 and 490/100,000 respectively). Annually in Tetovo 1,645 years of healthy life are lost, while in the Skopje region 3,936 (Table 7).

Table 7: Years of life lost due to premature mortality in terms of lung cancer mortality

Health endpoint - Lung cancer mortality, stressor PM _{2.5}									
Region	Estimated YLL (000) (WHO GHE 2016), >30 yr.	5-yrs mean PM _{2.5} (µg/m ³)	RR Macedonian exposures (10 µg/m ³)	Population Attributable Fraction (PAF)	Estimated burden of disease -YLL			Years of life saved if the annual mean of PM _{2.5} is reduced to 25 µg/m ³ (EU LV)*	
					#	LCL 95%CI	UCL 95%CI		
Skopje region	24.1	41.8	1.65	0.16	3,936	1,253	6,750	1,648	
Tetovo	24.1	81.7	2.65	0.07	1,645	402	3,639	1,269	
MKD	24.1	45.9	1.73	0.42	10,161	4,035	14,389	3,947	

*EU LV (EU Limit values, EU Directive 2008/50/EC on ambient air quality and cleaner air for Europe).

In Tetovo (about lung cancer), the number of saved years of healthy life will be five times greater when it is expressed on 100,000 population (Tetovo-1376, Skopje Region 263 and Macedonia 190 YLLs). The results of this methodological approach are summarised in Figure 1, where the association between the exposure concentrations of PM_{2.5} and the observed health outcomes is demonstrated.

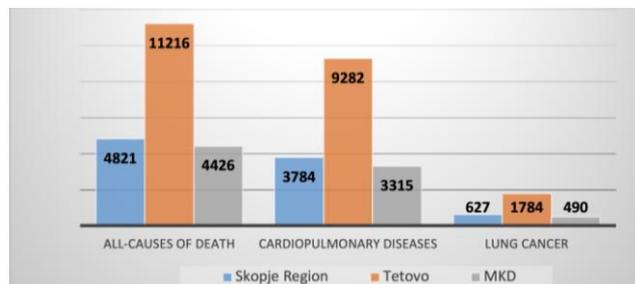


Figure 1: Years of life lost (YLL) due to current exposures to PM_{2.5} for the selected health outcomes

Health benefit estimates are graphically presented in Figure 2. As is expected, the health gain will be significantly higher in Tetovo in comparison to the Skopje Region and national estimates. The estimated health gain for the three selected health outcomes if EU limit values are reached, is 41-42% of the estimated burden in Skopje Region will be eliminated, and 74-77% in Tetovo.

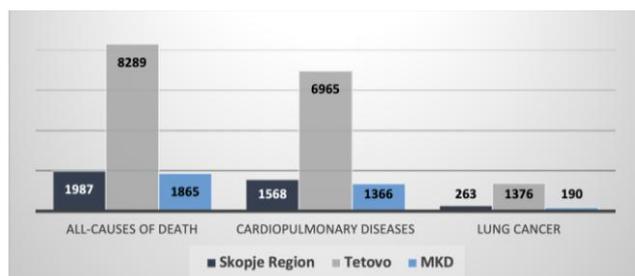


Figure 2: Health gains if the EU Directive limit values are met

Discussion

The use of the metrics for quantification of the environmental burden of diseases (DALY, YLL, YLD) was introduced by Murray and Lopez in 1996 for the World Bank GBD study [34]. In the first GBD study was estimated that almost a quarter of all diseases worldwide were caused by environmental exposure [35]. In Europe, national assessments of the environmental burden of disease (EBoD) have been carried out in several countries. The work by RIVM (the Netherlands) was one of the first systematic works in Europe in the field, which used the new DALY as a measure to compare the burden of different health outcomes in terms of population exposure to environmental stressors [36].

According to the European Environmental Agency (EEA) data for 2014, the number of premature deaths attributed to PM_{2.5} in the EU-28 is 4,278,000. In relative terms, when considered as YLL per 100,000 population, the biggest influences have been observed in the countries of Central and Eastern Europe where the highest concentrations of PM_{2.5} have been monitored such as Kosovo, Bulgaria, Macedonia, Poland, Serbia, Hungary, Romania, Greece, the Czech Republic and Slovakia [37]. The EBD study of six European countries assessed the total environmental burden of diseases related to nine stressors. The study estimated that particulate matters caused a loss of 1.8 million DALY annually, including 1.3 million healthy years of life lost due to premature death (73% of total DALYs). A total 67% of the estimated environmental burden of diseases in the EboD study is explained by the exposure of PM_{2.5}, making particulate air pollution the most important environmental risk factor affecting public health [38]. The study conducted for 2012 for the Skopje Region (without Sopiste, a rural municipality within Skopje agglomeration), estimated 16,209 attributable YLLs due to exposure of PM_{2.5} which represent a sum of years of life lost as a result of deaths that occurred before their expected lifespan. The number of years of life that could be prevented through appropriate policies to meet EU's limit values is 306 [39].

In this study, we estimated that at national level 91,851 years of healthy life (4426/100,000 population) are lost annually due to exposure of PM_{2.5} (the annual PM_{2.5} mean 45.9 µg/m³), which is significantly above the EEA estimates for 2014 (32,600 YLLs, expressed as a rate 1,578/100,000). This difference is primarily due to the difference in the population exposure concentrations. In 2014, the EEA estimates that the annual average of PM_{2.5} is 27.4 µg/m³, an average taken from urban background station only, while in our study calculations have been made for concentrations of PM_{2.5} as a fraction of PM₁₀ from all measuring stations in the country, as a five-year average (45.9 µg/m³ national mean, 41.8 µg/m³ for the Skopje Region and high 81.7 µg/m³ for Tetovo

(Table 2)).

Regarding the obtained differences with the Sanchez and collaborators study, the difference is due to the different methodological approach for estimation of YLL, where YLLs are calculated using a calculator for life tables developed by Spadaro J., which was later integrated into the AirQ + software used for the calculations. In our study, the global burden of disease due to all risk factors expressed through YLL has been obtained from the WHO database (WHO GHE DB, 2016). As well, we have included all rural municipalities in the estimates.

Estimated disease burden for all-cause natural mortality is highest in Tetovo, where 10,343 years of healthy life are lost annually because of the current exposure of PM_{2.5} (11,216/100,000). The Skopje Region estimates 30,256 YLL (4821/100,000) compared to the national average 91,851 YLL (4426/100,000 population) (Table 5). Calculated how many years of life are lost in terms of one lost life (in 2018 we estimated 1205 for Skopje Region and 265 for Tetovo), the average loss of life expectancy (expressed in years) is 25.1, while in Tetovo 39.0 [20].

The study has some limitations. Missing environmental data have been calculated from the averages in the respective months from the other years, as well as using a formula to estimate PM concentration as a fraction of PM₁₀ could be considered as a limitation of this study. The long-term effect of particulate air pollution observed the only through the YLL could also be a limitation because the burden of the years of life spent with some disability (expressed as YLD) is also significant.

These estimates could be a good basis for conducting a further study (economic analysis) to assess economic losses and expenditures associated with air pollution, as mortality or YLL represent the largest burden from the pollution, while DALYs as recommended by WHO is better to use for cost-effectiveness of a particular project or measure [40]. In terms of *health gains*, according to the COMEAP study the health benefits of reducing concentrations of the particulate matters analyzed through mortality are perceived immediately through a visible reduction in the number of deaths in the first or several years after some policy has been taken; or through long-term benefits that will be perceived by increasing the life expectancy of the population that will result with increment of the fraction of the elderly population [41]. Similarly, the benefits of policies that will reduce the exposure of the population to the PM reaching EU limit values will be most pronounced in cities with the highest concentrations of PM_{2.5}. Proportionally, for the three selected health outcomes reaching the EU Directive limit values will remove 41-42% of the estimated workload in the Skopje Region (expressed as YLL), 74-77% in Tetovo and 39-42% of the disease burden in the Republic of Macedonia.

In conclusion, the estimated impact of

particulate air pollution on mortality expressed with YLLs is significant and not negligible. The same applies to the health and well-being of the population if the EU or WHO limit levels are reached. The results of this type of assessments should be the basis of the decision-making process at all levels—from a local to a central level. The crucial element is national and local authorities to become aware of the magnitude of the problem and to take responsibility for prioritising activities, strengthening monitoring and control of ambient air pollution and consistently to enforce legislation without exceptions.

References

1. GBD 2015 Risk Factors Collaborators Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease. *Lancet*. 2016; 388:1659-1724. [https://doi.org/10.1016/S0140-6736\(16\)31679-8](https://doi.org/10.1016/S0140-6736(16)31679-8)
2. WHO Europe Data and statistics, 2015.
3. Landrigan PJ et al. The Lancet Commission on pollution and health. *Lancet*. 2018; 391(10119):462-512. [https://doi.org/10.1016/S0140-6736\(17\)32345-0](https://doi.org/10.1016/S0140-6736(17)32345-0)
4. Assembly UG. Transforming our world: the 2030 Agenda for Sustainable Development. New York: United Nations. 2015.
5. OECD (Organization for Economic Co-operation and Development) Environmental Outlook to 2050: The Consequences of Inaction India.
6. WHO Collaborating Centre for Air Quality Management and Air Pollution Control at the German Environment Agency Newsletter No. 58 - February 2017.
7. World Health Organization. Air quality guidelines: global update 2005: particulate matter, ozone, nitrogen dioxide, and sulfur dioxide. World Health Organization, 2006.
8. Correia AW, Pope III CA, Dockery DW, Wang Y, Ezzati M, Dominici F. The effect of air pollution control on life expectancy in the United States: an analysis of 545 US counties for the period 2000 to 2007. *Epidemiology (Cambridge, Mass.)*. 2013; 24(1):23-31. <https://doi.org/10.1097/EDE.0b013e3182770237> PMID:23211349 PMCID:PMC3521092
9. Dockery DW, Pope CA, Xu X et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med*. 1993; 329:1753-1759. <https://doi.org/10.1056/NEJM199312093292401> PMID:8179653
10. Pope III CA, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. 2004; 109(1):71-7. <https://doi.org/10.1161/01.CIR.0000108927.80044.7F> PMID:14676145
11. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *The Lancet*. 2002; 360(9341):1203-9. [https://doi.org/10.1016/S0140-6736\(02\)11280-3](https://doi.org/10.1016/S0140-6736(02)11280-3)
12. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016; 388:1459–544. [https://doi.org/10.1016/S0140-6736\(16\)31012-1](https://doi.org/10.1016/S0140-6736(16)31012-1)
13. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R, Feigin V. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *The Lancet*. 2017; 389(10082):1907-18. [https://doi.org/10.1016/S0140-6736\(17\)30505-6](https://doi.org/10.1016/S0140-6736(17)30505-6)
14. WHO (World Health Organization) Review of evidence on health aspects of air pollution—REVIHAAP project. Technical report, 2013.
15. WHO (World Health Organization) Health risks of air pollution in Europe—HRAPIE project. Recommendations for concentration–response functions for cost–benefit analysis of particulate matter, ozone and nitrogen dioxide, 2013.
16. APHEKOM Summary Report. Improving Knowledge and Communication for Decision Making on Air Pollution and Health in Europe, 2011.
17. WHO Press release No 221. IARC statement.
18. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Outdoor air pollution. Lyon (FR): International Agency for Research on Cancer; 2016. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 109, 2016).
19. Meisner C, Gjorgjev D, Tozija F. Estimating health impacts and economic costs of air pollution in the Republic of Macedonia. *South Eastern European Journal of Public Health*. 2015; 4(1).
20. Dimovska M. Application of methods for risk assessment in conditions of high urban air pollution in the Republic of Macedonia. Doctoral thesis. Medical Faculty Skopje. Ss Cyril and Methodius University Skopje. 2019.
21. Macedonian Environmental Information Center. MoEPP. Macedonian Air Quality Assessment Report for the period 2005–2015.
22. Murray CJL, Lopez AD for the World Health Organization the World Bank Harvard University Press, Cambridge, MA; 1996.
23. Mathers CD, Vos T, Lopez AD, Salomon J, Ezzati M. World Health Organization Global Program on Evidence for Health Policy National burden of disease studies: a practical guide. (2nd edn.), 2001.
24. Martuzzi M, Mitis F, Iavarone I, Serinelli M. Health Impact of Ozone in 13 Italian Cities; *Europe PMC*: London, UK, 2013.
25. Landrigan JP, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu N, et al. The Lancet Commission on pollution and health. *The Lancet Commissions*. 2018; 391(10119):462-512. [https://doi.org/10.1016/S0140-6736\(17\)32345-0](https://doi.org/10.1016/S0140-6736(17)32345-0)
26. Rockhill B, Newman B, Weinberg C. Use and Misuse of population attributable fractions. *Am J Public Health*. 1998; 88(1):15-19. <https://doi.org/10.2105/AJPH.88.1.15> PMID:9584027 PMCID:PMC1508384
27. Prüss-Üstün A, Wolf J, Corvalán C, Bos R, Neira M. Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks. World Health Organization; 2016. PMID:27783646
28. Drzhaven zavod za statistika. Statistichki godishnik na Republika Makedonija, 2018.
29. Zone and Agglomeration in the Republic of Macedonia. In: Air Quality Assessment Report. Ministry of Environment and Physical Planning (MoEPP). Republic of Macedonia, 2012.
30. Fann N, Bell ML, Walker K, Hubbell B. Improving the linkages between air pollution epidemiology and quantitative risk assessment. *Environ Health Perspect*. 2011; 119(12):1671–5. <https://doi.org/10.1289/ehp.1103780> PMID:21816702 PMCID:PMC3261990
31. Héroux M-E, Anderson HR, Atkinson R, et al. Response to: Premature deaths attributed to ambient air pollutants: let us interpret the Robins–Greenland theorem correctly. *International Journal of Public Health*. 2017; 62(3):339-341. <https://doi.org/10.1007/s00038-017-0956-7> PMID:28299391 PMCID:PMC5364256

32. Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, Kaufman JD. Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environmental health*. 2013; 12(1):43. <https://doi.org/10.1186/1476-069X-12-43> PMID:23714370 PMCID:PMC3679821
33. Pope CA, Burnett RT, Thun MJ, et al. Lung Cancer, Cardiopulmonary Mortality, and Long-term Exposure to Fine Particulate Air Pollution. *JAMA: the journal of the American Medical Association*. 2002; 287(9):1132-1141. <https://doi.org/10.1001/jama.287.9.1132> PMID:11879110 PMCID:PMC4037163
34. Murray CJ, Lopez L, Alan D. World Health Organization, World Bank & Harvard School of Public Health. (1996). *The Global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: summary* / edited by Murray CJ, Alan D. Lopez L. Geneva: World Health Organization.
35. Prüss-Üstün A, Corvalán C. Preventing disease through healthy environments. Towards an estimate of the environmental burden of disease. WHO, 2006. PMCID:PMC1392231
36. Hollander AE, Melse JM, Lebrecht E, Kramers PG. An aggregate public health indicator to represent the impact of multiple environmental exposures. *Epidemiology-Baltimore*. 1999; 10(5):606-17. <https://doi.org/10.1097/00001648-199909000-00030>
37. European Environmental Agency. *Air Quality in Europe - 2017* report. Available at: <https://www.eea.europa.eu/publications/air-quality-in-europe-2017>.
38. Hänninen O, Knol A. (Eds.) EBoDE-Report. Environmental Perspectives on Environmental Burden of Disease. Estimates for Nine Stressors in Six European Countries. National Institute for Health and Welfare (THL), Report 1/2011. 86 pages and 2 appendixes. Helsinki, Finland, 2011.
39. Martinez GS, Spadaro JV, Chapizanis D, Kendrovski V, Kochubovski M, Mudu P. Health Impacts and Economic Costs of Air Pollution in the Metropolitan Area of Skopje. *International journal of environmental research and public health*. 2018; 15(4):626. <https://doi.org/10.3390/ijerph15040626> PMID:29596347 PMCID:PMC5923668
40. Narain U, Chris S. *Methodology for evaluating the effects on the health of air pollution: discussion of the challenges and proposed solutions*. World Bank, Washington, 2016. License: Creative Commons Attribution-Share Alike 3.0 Unported source CC BY 3.0 IGO, 2016.
41. COMEAP Report (Committee on the Medical Effects of Air Pollutants). *The mortality effects of long-term exposure to particulate air pollution in the United Kingdom*, 2010.